UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,096	12/11/2003	Steven Goldstein	11930-135	7988

757 7590 05/23/2005

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, IL 60610

EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,096	GOLDSTEIN ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-110* is/are pending in the application.

4a) Of the above claim(s) *1-48 and 66-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-65 and 73-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/7/05 and 1/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

9-6-0

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, claims 49-65 in the reply filed on 4/8/05 is acknowledged. The examiner also notes the addition of new claims 73-110, which depend from claim 49. The traversal of the restriction requirement is on the ground(s) that Groups III and IV are drawn to the same subject matter and are classified together in 435/1.3. The applicant's arguments have been fully considered, but they are not persuasive.

Group III requires that a solution and the tissue be frozen together; Group IV requires only that the tissue be combined with a solution and be frozen in a separate step, but not specifically that the two be frozen together. Additionally, the method of Group IV requires the use of a different solution than that recited by Group III. The methods do not have the same steps or require the same starting products and are clearly distinct from each other.

At the core of the applicants' traverse to the restriction requirement, however, is the issue of search burden. Applicants assert that since most patents require a search of more than one class and subclass, presumably without burden, searching each and every one of claims 49-110 would not burden the examiner. In fact, burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement and double patenting issues.

Searching the instant two patentably distinct inventions would, in fact, impose a serious burden on the examiner. If applicants admit on the record that Groups III and IV are obvious over one another, the Groups will be rejoined, since a single search would suffice for all Groups. **By so admitting, applicants stipulate that if a reference is considered prior art over one Group, it shall be considered prior art over both Groups.**

The requirement is still deemed proper and is therefore made FINAL. Claims 66-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Examination will continue at this point on claims 49-65 and 73-110 ONLY.

Specification

Applicant is reminded of the proper content, language and format of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and **should include that which is new in the art** to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;

(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. **The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided.** The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. **It should avoid using phrases which can be implied**, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The disclosure is objected to because of the following informalities: The numbering of paragraphs is inconsistent (pages 1-3 use three-digit numbers, while pages 4-24 use four-digit numbers). Appropriate correction is required.

The use of the trademark "KOLLIDONE" has been noted in this application, for example in paragraph 0075. It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Currently, the use of the word "radical" is confusing, as it is not clear whether it refers to one component of the claimed invention or to the characterization of the instant inventive concept.

Claim Objections

Claim 73 is objected to because the word "fascia" is misspelled at line 4 and the word "dura mater" is misspelled at line 5. Claim 93 is objected to because the word "agarose" is misspelled at line 3. Claim 103 is objected to because the word "flavonoids" is misspelled at line 4. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49-62, 64, and 73-110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 recites a method for forming a cryopreserved tissue, but the claim does not recite a cryopreservation step *per se*, but simply a "freezing" step. The term "cryopreservation", as implied by the specification and accepted by skilled artisans, refers specifically to freezing to a "cryogenic temperature", *i.e.* a very low temperature, at least at the temperature of dry ice (-79°C). A water-based solution such as that claimed might freeze at a temperature significantly higher than -79°C; it is not clear, therefore, how the **claimed** process of claim 49 results in a cryopreserved tissue. Clarification is required. Because claims 50-62, 64, and 73-110 depend from indefinite claim 49 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 53 is confusing in that it does not particularly set forth that which is being claimed. Claim 53 recites thawing tissue after it has been subjected to "extended storage". It is not clear how much time must elapse to be considered "extended" time. Clarification is required.

Claim 58 is confusing in that it recites a temperature within "about +/- 3°C". It is not clear what degree of deviation is tolerated by the claim. Clarification is required.

Claim 73 is confusing in that it recites that the "tissue" may be selected from a group comprising "blood cells" and "blood proteins". Cells and proteins are not tissues. Clarification is required.

Claim 80 is confusing in that it requires that the "tissue" be "decellularized". Since tissue is, by definition, a collection of cells that perform a particular function, it is not clear how a substance can be considered tissue if it does not comprise cells. Clarification is required.

Claim 82 is confusing in that it recites a buffer that is "isotonic" but does not set forth a point of comparison for this relative term. Clarification is required.

Claim 93 is confusing in that it recites "long-chain polymers" without particularly pointing out either the character of the monomer units or the criteria for evaluating length. In addition, claim 93 recites a long list of constituents and "derivatives thereof" without limiting the manner in which a given compound might be related to the recited constituents or, indeed, which related compounds are included or excluded by the claim. Clarification is required.

Claim 93 is also confusing in that it recites both a broad genus ("polysaccharides") and narrow species within the genus (e.g., "agarose"), making it impossible to determine the scope of the claim. Clarification is required.

Claim 94 also recites "derivatives" of PVPs and hydroxyethyl starches without limiting the manner in which a given compound might be related to the recited constituents or, indeed, which related compounds are included or excluded by the claim. Clarification is required.

Claim 98 is confusing in that it recites both broad genuses ("alcohols", "glycols", "aldoses", and "ketoses") and narrow species within these genuses (e.g., "mannitol", "ethylene glycol", "glucose" and "fructose"), making it impossible to determine the scope of the claim. Clarification is required.

Claim 103 is confusing in that it recites both broad genuses ("carotenoids" and "flavonoids", "alpha-lipoic acids", "water-soluble tocopherol derivatives") and narrow species (e.g., "1-ascorbic acid" and "nicotinic acid"), making it impossible to determine the scope of the claim. Claim 104 has identical problems. Clarification is required.

Claim 103 is further confusing in that it recites "derivatives" and "analogs" of the recited constituents without limiting the manner in which a given compound might be related to said constituents or, indeed, which related compounds are included or excluded by the claim. Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 49, 50, 59, 61-65, 73, 81-90, 98, 101-106, and 108 are rejected under 35 U.S.C. 102(b) as being anticipated by Fisher et al. (1994, U.S. Patent 5,328,821; reference A). The claims are drawn to a method for forming a cryopreserved tissue comprising providing a solution comprising water, a biocompatible buffer, a cell-impermeant constituent, a cell-permeant constituent, and a radical scavenger; combining said solution with a tissue; and freezing the resulting combination. In some dependent claims, the combination is packaged. Some dependent claims set forth a temperature for freezing. In some dependent claims, the solution maintains the pH within a specific range. In some dependent claims, the bio-compatible buffer is selected from a list, has a concentration within a specific range (88-89), and comprises sodium chloride. In some dependent claims, the cell-permeant constituent is selected from a list and has a concentration within a specific range. In some dependent claims, the radical scavenger is selected from a list.

U.S. '821 teaches a method for cryopreserving liver slices in V-7 solution comprising combining liver slices with V-7 solution and lowering the temperature of the resulting combination to –196°C, a temperature at which the tissue is stable for years (column 11, lines 4-14). V-7 solution (see Table 2) maintains a pH of 7.4 and comprises water, phosphate-buffered saline (25mM phosphate), cell-impermeant constituents (gluconate and saccharate, 60mM each), cell-permeant constituents (glucose and fructose, 2mM each), and a radical scavenger (ascorbic acid potassium salt, 5mM). V-7

solution further comprises sodium succinate and magnesium chloride (2mM each); it therefore inherently comprises sodium chloride.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 49, 50, 52-65, 73, 81-90, 98, 101-106, 108, and 110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (reference A) taken in view of Freeman, Jr. (1989, U.S. Patent 4,798,611; IDS of 1/31/05). The claims are drawn to a method substantially as described above. In some dependent claims, the cryopreserved tissue is irradiated with ionizing radiation, for example gamma radiation, after cryopreservation. In some dependent claims, a particular amount of radiation is used, for a particular time.

As detailed above, U.S. '821 teaches a method for cryopreserving liver slices in V-7 solution comprising combining liver slices with V-7 solution and lowering the temperature of the resulting combination to –196°C, a temperature at which the tissue is stable for years. U.S. '821 does not teach irradiating the tissue at any time.

U.S. '611 teaches a method for the sterilization of bovine tendons comprising irradiating said tendons with 2,000,000-5,000,000 rads of sterilizing high-energy gamma radiation from ^{60}Co decay (column 5, lines 13-24). U.S. '611 further suggests that an equivalent high-energy radiation source may be electron beam acceleration (column 4, lines 15-19).

U.S. '611 does not recite or imply packaging, so it is silent as to whether irradiation should be carried out before or after any packaging of cryopreserved tissue; however, the order in which these steps are performed is clearly a matter of routine optimization. M.P.E.P. § 2144 recites, "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally

available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law... If the facts in a prior legal decision are sufficiently similar to those in an application under examination, the examiner may use the rationale used by the court." In *In re Burhans, 154 F.2d 690, 69 USPQ 330* (CCPA 1946), the court found that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results.

A person of ordinary skill in the art would have had a reasonable expectation of success in sterilizing the cryopreserved tissue of U.S. '821 with the gamma-irradiation step of U.S. '611 because U.S. '611 teaches that gamma irradiation efficiently sterilizes tissue and tissue matrices (column 4, lines 20-26) and that said irradiation does not degrade the tissue so treated (column 5, lines 18-24). The skilled artisan would have been motivated to use the irradiation step of U.S. '611 on the cryopreserved tissue of U.S. '821 for the expected benefit of preventing microbial infestation of said tissue, allowing it to be used later for transplantation procedures; in fact, U.S. '611 teaches that the irradiation process decreases the potential antigenicity of the treated tissue (column 4, lines 55-60).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to treat the cryopreserved tissue of U.S. '821 with the gamma irradiation of U.S. '611 because U.S. '611 teaches that said irradiation provides so-treated tissue numerous benefits as they pertain to downstream applications.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 49-65 and 73-110 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. '821 taken in view of U.S. '611 as applied to claims 49, 50, 52-65, 73, 81-90, 98, 101-106, 108, and 110 above, and further in view of Carstairs et al. (1997, U.S. Patent 5,677,019; reference B), Demetriou et al. (2000, U.S. Patent 6,140,123; reference C), Lawrence et al. (1979, U.S. Patent 4,155,331; reference D), Chrisope (1994, U.S. Patent 5,279,964; reference E), and Malfroy-Camine et al. (1995, U.S. Patent 5,403,834; reference F). The claims are drawn to a method as described above. In some dependent claims, the bio-compatible buffer, cell-impermeant constituent, cell-permeant constituent, and radical scavenger are selected from a list and are each present in a particular concentration.

As detailed above, U.S. '821 teaches a method for cryopreserving liver slices in V-7 solution comprising combining liver slices with V-7 solution and lowering the temperature of the resulting combination to –196°C. U.S. '611 teaches a method for the sterilization of bovine tendons comprising irradiating said tendons with sterilizing high-energy gamma radiation. Neither U.S. '821 nor U.S. '611 addresses each and every embodiment for the bio-compatible buffer, cell-impermeant constituent, cell-permeant constituent, and radical scavenger recited in the dependent claims.

U.S. '019 teaches a method for preserving tissue comprising mixing the tissue with a preserving solution comprising propylene glycol, 1,4-butanediol, isopropanol, and water (Example 3).

U.S. '123 teaches cryopreservation using various bio-compatible buffers (column 7, lines 30-40), radical scavengers (column 7, lines 21-29), cryopreservatives (column

8, lines 1-12), and constituent salts (column 7, lines 4-11). U.S. '123 further teaches various embodiments of freezing protocols (column 8, line 66 through column 10, line 65).

U.S. '331 teaches that acceptable cryoprotectants include glycerol, glucose, fructose, DMSO, and polyvinylpyrrolidone (column 5, lines 20-27).

U.S. '964 teaches a cryoprotectant solution comprising carbohydrate (*e.g.* dextrose), a reducing agent (*i.e.* radical scavenger; sodium ascorbate), and a preservative (*i.e.* an alcohol, including isopropanol).

U.S. '834 teaches that radical scavengers (including tocopherol, ascorbate, glutathione, and N-acetylcysteine) enhance cryopreservation of cells, tissues, and organs by increasing the viability of recovered specimens (column 6, lines 7-39).

The selection of bio-compatible buffer, cell-impermeant constituent, cell-permeant constituent, and radical scavenger and the concentration of each in the claimed cryopreservation clearly would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that the numerous bio-compatible buffers are functionally equivalent to each other, as are each of the cell-impermeant constituents to each other, and so on. Absent a showing of unexpected results, the claimed embodiments merely recite various obvious modifications of cryopreservation solutions well known in the art. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute any of the recited bio-compatible buffers, cell-

impermeant constituents, cell-permeant constituents, and radical scavengers into the solution of U.S. '821 because U.S. '019, U.S. '123, U.S. '331, U.S. '964, and U.S. '834 teach that these and other embodiments are art-accepted equivalents for each other.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

No claims are allowed. No claims are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lora E Barnhart

SANDRA E. SAUCIER
PRIMARY EXAMINER